PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Eric OLSON *et al.*

Serial No.: 09/061,417

Filed: April 16, 1998

For: METHODS AND COMPOSITIONS FOR THERAPEUTIC INTERVENTION IN CARDIAC HYPERTROPHY

Group Art Unit: 1642

Examiner D. Minh Tam

Atty. Dkt. No.: MYOG:029US/SLH

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

July 24, 2002
Date

Steven L. Highlander

DECLARATION OF RICK GORCZYNSKI UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Rick Gorczynski, do declare the following:

1. I am currently hold the position of Vice President, Research & Development at Myogen, Inc., licensee of the above-captioned application. My education and training includes an undergraduate degree in Biological Sciences from Cornell University and a Ph.D. in Cardiovascular Physiology from the University of Virginia, School of Medicine. I have worked since 1976 in the pharmaceutical industry, primarily in the cardiovascular drug discovery field. During my 25 years in the industry I have conducted and/or supervised

research directed at a variety of cardiovascular diseases including heart failure (acute and chronic), myocardial infarction, cardiac dysrhythmia, hypertension, renal disease, hyperlipidemias and thrombosis disorders. For the past 4 years I have been exclusively engaged in the discovery and validation of molecular drug targets for use in drug discovery in the filed of heart failure. I am intimately familiar with the use of transgenic mice in the field of cardiac research and heart failure. A copy of my *curriculum vitae* is attached.

2. I am also familiar with the level of skill of scientists working in the field of cardiology and molecular biology as of the priority date of the referenced application. I consider one of ordinary skill in the art in this field of study to have a Ph.D. in biochemistry, chemistry, molecular biology, pathology or other related field, or an M.D., with 1-3 years of post-graduate study.

3. I have reviewed the specification and pending claims 1, 4, and 9 for the above-referenced case. The specification refers to the use of transfected cells and transgenic mice where NF-AT3 is either overexpressed (transfected cells) or continuously activated (transgenics) as a model for hypertrophy studies that are then held out as subsequently relevant for human studies. More specifically the specification refers to NF-AT3 transgenes lacking one or more phosphorylation sites present in wild-type NF-AT3, NF-AT3 transgenes lacking all the phosphorylation sites of the wild-type protein, and NF-AT3 transgenes lacking amino acids 1-137 of the wild-type NF-AT3 protein.

4. The inventors' paradigm, as defined through the transgenic models, was that activated calcineurin would directly bind to and dephosphorylate cytoplasmic NF-AT3. The

dephosphorylated NF-AT3 would then translocate into the nucleus where it would act as a transcription factor along with GATA-4, leading to induction of hypertrophic genes. It has not yet been shown, as the examiner correctly points out, that NF-AT3 is constitutively active or in a more active state in the hearts of hypertrophic patients. Nonetheless, NF-AT3 presents itself as an attractive candidate for therapy in cardiac hypertrophy. To that end, the inventors have targeted NF-AT3 both directly and indirectly to inhibit the onset of the transcription of hypertrophic genes.

5. I have reviewed the enclosed article by Ritter *et al.*, entitled "Calcineurin in Human Heart Hypertrophy," *Circulation*, 105:2265-2269 (2002) which supports the inventors' claims relating to NF-AT3 as a therapeutic target. The Ritter *et al.* authors set out to validate the observations made in transgenic mouse models by studying enzymatic activity and protein expression in cardiac tissue from human patients suffering from hypertrophic obstructive cardiomyopathy. While the article focuses more on the data regarding calcineurin levels in the hypertrophic hearts, the researchers also studied NF-AT2 phosphorlyation levels in normal and hypertrophic heart tissue.

Ritter *et al.* showed that, in naturally hypertrophic tissues, NF-AT2 migrated at a higher rate on a 6% SDS gel, "compared with normal heart and identical to the NF-AT migration velocity of normal heart extracts treated with additional external calcineurin" (p. 2267), providing *in vivo* evidence from a human clinical setting of an altered NF-AT phosphorlyation state in hypertrophied myocardium. This shows that NF-AT2, is in a more active, dephosphorylated form in the human hypertrophic heart, and also strongly implicates a similar finding for NF-AT3. Moreover, it validates the present inventors' notion of targeting NF-AT3 therapeutically to combat hypertrophy by interfering with the

NF-AT3 transcriptional cascade, whether by direct blocking (as in binding a molecule to NF-AT3) or by indirect effects (targeting the purported NF-AT3/GATA-4 complex).

6. With regard to the issue of using transfected cells to elucidate the interaction between NF-AT3 and GATA4, I have reviewed the attached scientific publications entitled "The Zinc Finger-containing Transcription Factors GATA-4, -5, and –6" (*J. Biol. Chem.* 275:50, 38949-38952, 2000), and "Remodeling muscles with calcineurin," (*BioEssays* 22:510-519, 2000). Based on the results set forth in these papers, it is clear to me that a person of ordinary skill (as defined above) would recognize that the art currently accepts that NF-AT3 does indeed interact with GATA-4, although the has not been shown directly. Perhaps the best information on this point comes from the latter paper, a mini-review of the state of the art, published over a year and a half ago. This article states that "GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT)" (p. 38951; also see Molkentin, *Cell* 93, 215; and Morin, *EMBO J.*, 19, 2046).

In conclusion, though no single experiment demonstrates a physical interaction between GATA-4 and NF-AT3, the aforementioned authors, as well as those of ordinary skill in the art in the field of cardiac biology, believe that such an interaction takes place. Further, it is my opinion that targeting this interaction using the approaches set forth in the present specification, with which is am quite familiar, is a valid approach to the treatment of hypertrophy. In particular, the use of GATA-4 mimetics and other small molecules that would interrupt the NF-AT3/GATA-4 interaction would be expected to interfere with NF-AT3's stimulation of the hypertrophic genes, providing a benefit to the patient.

7. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

July 3, 2007
Date

Richard Gorczynski
Rick Gorczynski, Ph.D.

CURRICULUM VITAE

RICHARD J. GORCZYNSKI, Ph.D.
5224 Pinehurst Drive
Boulder, CO 80301
home (303) 516-0516
work (303) 464-5224

PROFESSIONAL EXPERIENCE

12/98-present
Vice President, Research and Development, Myogen Inc, Westminster, Colorado
Responsibilities

- Corporate Officer and member of the Myogen Executive Management Team
- Lead R&D activities focused on clinical development of one Phase II and one Phase III stage therapeutics for treatment of heart failure and related disorders; use of genomic, proteomic and biological techniques for identification of novel, disease-modifying compounds for reversal and prevention of heart failure; validation of molecular targets for drug discovery; identification of novel diagnostic markers for cardiac hypertrophy and heart failure
- Project Team Leader for Enoximone P.O. Development (until 1/00)
- Project Steering Committee member for BSF 208075
- Project Team Leader for Myosin Heavy Chain Project (collaboration between Myogen and a big pharma company)

Accomplishments

- In collaboration with Myogen scientific and medical advisory boards, established the company's Research Plan; established Target Validation techniques, HT Screening for the Company; built the R&D Group; managed external collaborations resulting in the identification of new technology for the Company.
- Project Plans for two Projects established: enoximone P.O. and Myosin Heavy Chain
- Planned and completed two successful meetings with the FDA Cardiorenal Division; resulted in agreement to proceed to Phase III with a heart failure therapeutic (enoximone); achieved alignment with the Agency on endpoints for four Phase II studies, product labelling language and scope of NDA.

6/98-11/98
Vice President, Research and Development and Boulder-Site Manager, Baxter, Hemoglobin Therapeutics Division, (Post-Baxter acquistion of Somatogen), Boulder, Colorado
Responsibilities

- Member of the Hemoglobin Therapeutics Division Management Team

- Lead Research and development activities at the Boulder-Site focused on the biological support of a Phase III-stage hemoglobin product candidate, DCLHb, research and development support for a Phase II-stage hemoglobin product candidate, rHb1.1 and research and development activities related to the discovery and advancement to clinical evaluation of a Second Generation hemoglobin product candidates
- Manage the Boulder-Site administratively, including facilities, safety, MIS and communications for R&D, Operations, Clinical, HR and Finance.

Accomplishments

- Defined new Boulder-Site organization in collaboration with the hemoglobin Therapeutics Division management team
- Identified several novel Second Generation hemoglobin product candidates

12/94 -6/98
Vice President, Research and Development, Somatogen, Inc., Boulder, CO
Responsibilities

- Corporate Officer and member of the Executive Management Group.
- Lead Research and Development activities at Somatogen; focused on 1) commercialization of lead product, Recombinant Human Hemoglobin (rHb 1.1) for oxygen-delivering and hematopoietic therapeutic indications 2) discovery and development of Second Generation recombinant hemoglobin products 3) development of non-hemoglobin technologies.
- Manage and coordinate Departments of Molecular Biology, Protein Engineering, Hemoglobin Research/Protein Chemistry, Pharmacology/Toxicology, Molecular Computation, Analytical Development, Purification Development, Formulation Development, and Fermentation Development (total of 65-70 people).

R&D Accomplishments

- In conjunction with the other Corporate Officers, positioned Somatogen for acquisition by Baxter Heathcare and prepared and presented the key technology summaries which lured Baxter to the table and eventually lead to an acquisition of Somatogen.
- Developed bioprocess for making clinical grade (GMP) rHb1.1 with successful scale-up demonstrating achievement of commercial expression and downstream yield targets; includes construction of host vector and strain, fermentation process, recovery and downstream purification system and associated analytical characterization; some of this was accomplished in collaboration with Eli Lilly and Co., our strategic corporate partner at that time.
- Advanced the understanding of hemoglobin biological effects including efficacy (oxygen delivery to tissue and potency), and safety related biologic effects; this work completed in support of commercial development of rHb1.1 and extended to the discovery of novel hemoglobin products.
- Initiated research on a promising new indication for rHb1.1: tumor radiation therapy sensitization.
- Initiated a drug-discovery project to identify new generation recombinant hemoglobin with enhanced therapeutic attributes; over 600 variant recombinant and

chemically modified/conjugated/cross-linked molecules constructed in three years; several lead molecules are undergoing advanced biological evaluation to ascertain suitability for human clinical testing. All have significantly improved properties.
- Three/four fold increases in rHb expression levels have been achieved (relative to commercial targets for rHb1.1).
- Completed several studies investigating the level of hematopoietic activity of rHb1.1 and other recombinant hemoglobins.
- Supervised preclinical discovery and development of a novel, in-licensed platelet substitute.

4/93 -12/94
Senior Director, Drug Discovery, Searle, Skokie, IL
Responsibilities
- Supervise the Cardiovascular Discovery Research Department (approximately 50 scientists; two sites: Skokie and St. Louis) with primary emphasis on atherosclerosis, thrombosis, arrhythmia, congestive heart failure and hyperlipidemia.
- Coordinate the process by which compounds from the Discovery Department are selected for, and transferred into, the Development Pipeline.
- Member R/D Executive Committee, Research Executive Committee and Development Executive Committee.
- Skokie Discovery Site Manager for facilities, safety and space administration.
- R/D liaison to the Corporate Licensing group.

Accomplishments
- Department Charter and Long Range Research Plan established.
- Five new Ph.D. hires in 1993 with backgrounds representing new directions in cardiovascular research (atherosclerosis/thrombosis/diabetes).
- Directed the design of a process by which Searle R/D will select Discovery stage compounds for formal Development; process consists of early toxicity, formulation, pharmacokinetic and chemical development studies of candidate molecules to optimize selection and the completion of critical analysis (development plan, marketing and financial) to support informal discussions on what to develop.
- Advanced new antiplatelet and antithrombotic agents into development (7/94); two antiplatelet compounds advanced to Phase III clinical development

8/89 - 4/93
Senior Director, Scientific and Product Affairs, Licensing/Business Development, Searle, Skokie, IL
Responsibilities
- Identification and follow-up of license and business development opportunities, with particular emphasis on Japan. Technical evaluation of all product license candidates.
- Manage process for full technical, medical and marketing review of candidates.
- Coordinate design of Development and Commercialization Plans for in-license candidates.
- Presentation of licensing opportunities to Searle top-management.

- Liaison between Licensing and Searle R/D.

Accomplishments:

- Two development collaborations initiated.
- One compound in-licensed (antidiabetic).

1/86 - 8/89

Director, Department of Cardiovascular Diseases Research, Searle, Skokie, IL

Responsibilities

- Supervise product discovery, chemical and biological research in the cardiovascular field with primary emphasis on hypertension, atherosclerosis, thrombosis and arrhythmia (staff: 45).

Accomplishments

- Four compounds into development (antihypertensive, and three antiplatelet agents).
- Two compounds in clinical study: antiarrhythmic and hypolipidemic.

9/85 - 1/86

Director, Biological Research Department, Searle, Skokie, IL

Responsibilities

- Supervised product discovery, biological research in four areas: cardiovascular, CNS, gastrointestinal and autocoid mediated diseases (staff: 80).
- Department was reorganized 1/86 following restructuring of all R/D after Monsanto takeover of Searle.

8/83 - 9/85

Section Head Pharmacology, American Critical Care (Division of Baxter Travenol Corp) (formerly Arnar-Stone Laboratories), McGaw Park, IL

Responsibilities

- Supervised drug discovery, biological research in the cardiovascular, ophthalmic and CNS areas including beta-blockers, positive inotropic asgents, antiarrhythmic agents, antiglaucoma agents and antiepileptic agents (staff: 13).

Accomplishments

- Five compounds into development (two beta-blockers, one antiglaucoma, one antiarrhythmic and one antiepileptic).
- Four IND's and one NDA (with approval).

9/80 - 8/83

Group Leader, American Critical Care (Division of American Hospital Supply Corp.) McGaw Park, IL,

Responsibilities

- Supervised drug discovery, biological research in the cardiovascular area (beta-blockers, cardiotonics and alpha blockers).

11/78 - 9/80
Senior Research Investigator, Arnar-Stone Laboratories (Division of American Hospital Supply Corp.), McGaw Park, IL,
Responsibilities

- Drug discovery in field of dopamine analogues and beta adrenergic receptor antagonists.

9/76 - 11/78
Research Investigator, Arnar-Stone Laboratories, McGaw Park, IL
Responsibilities

- Drug discovery in field of dopamine analogues and beta adrenergic receptor antagonists.

DRUG DEVELOPMENT EXPERIENCE

- Project Team Leader: enoximone P.O.; Phase II for treatment of ultra-advanced heart failure (myogen).
- Project Team Leader: Second Generation recombinant hemoglobin project (Somatogen).
- Designed the process used to select compounds for formal Development and Clinical Study (Searle).
- Liaison to Development Project Teams for all cardiovascular compounds accepted for development (Searle).
- Project Team Leader (American Critical Care).
- Coordinate design of Development and Commercialization Plans for in-license candidates.
- Development of an ultra-short acting beta-blocker - responsible for organizing and tracking development of a novel compound through all stages of preclinical development (raw material supplies, pharmacology, drug metabolism/pharmacokinetics, analytical assays, formulation, stability, etc.) and initial clinical trials.
- Member of three other project teams which are responsible for the development of a vasodilator, an antiarrhythmic agent and another ultra-short acting beta-blocker.

EDUCATION

1976 Ph.D., Physiology
University of Virginia
School of Medicine, Department of Physiology
Charlottesville, Virginia

Dissertation: The Microcirculatory Basis of Functional Hyperemia in Striated Muscle (University Microfilms #76-25012)
Thesis Advisor: Brian R. Duling, Ph.D., Professor of Physiology

1970 B.A., Biological Sciences
Cornell University
Ithaca, New York

TRAINING

1996 Somatogen: Performance Management System

1995 Somatogen: Project Management

1990 Searle: Introduction to Financial Analysis in Business (AMA)

1989 Searle: Introduction to Licensing (LES)

1989 Searle: Decision Making Skills: Consensus

1986 Searle: Interview Selection Skills

1986 Searle: Personnel Management System Training

1983 American Hospital Supply: Corporate Middle Management Course

1981 American Management Association: Project Management

1980 American Hospital Supply: Management Style and Effectiveness Training

AWARDS

American Critical Care President's Award for Scientific and Technical Excellence - 1979

Runner-up for American Critical Care President's Award for Scientific and Technical Excellence - 1978

PROFESSIONAL ACTIVITIES

Member, Editorial Board of the Journal of Cardiovascular Pharmacology - 1984 to 1994

Ad Hoc Reviewer for Microvascular Research, the American Journal of Physiology and the Journal of Pharmacology and Experimental Therapeutics, Blood

SOCIETIES

International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology (Scientific Steering Committee)
American Society for Pharmacology and Experimental Therapeutics
American Association for Advancement of Science
International Society for Heart Research
Licensing Executives Society
American Heart Association

PATENTS

Novel therapeutic and diagnostic agents for treatment of heart failure. Applied May, 1999.

Epoxy-Steroidal Aldosterone Antagonist and Angiotensin II Antagonist Combination Therapy for Treatment of Congestive Heart Failure. WO96/40257

SEMINARS

1. Department of Physiology, University of Virginia, Fall 1976. "The microcirculatory basis of functional hyperemia in striated muscle".

2. Department of Physiology, Medical College of Wisconsin, Fall 1977. "The microcirculatory basis of functional hyperemia in hamster striated muscle".

3. Cardiovascular Discussion Group, Skokie, IL, Fall 1982. "Mechanisms of inotropic selectivity".

4. Esmolol Symposium, Spring 1985. "Basic pharmacology of esmolol".

5. Kureha Chemical Industry, Tokyo, Fall 1989. "Platelet GPIIb/IIIa: a new target for discovery of novel antiplatelet agents".

6. University of Virginia, Graduate Study Colloquium, Winter, 1994. "Job Opportunities in the Pharmaceutical Industry."

7. IBC Conference Blood Substitute, 1996. "Measurement of the Efficacy of Hemoglobin-based Oxygen Carriers

8. International Symposium on Intensive Care and Emergency Medicine, Brussels, 1997. Preclinical update on rHb1.1

9. Tokyo Blood Substitutes Conference, 1997. "Comparison of Optro with Whole Blood using 31 P-NMR Spectroscopy"

PUBLICATIONS

1. Spath, J.A., Gorczynski, R.J. and Lefer, A.M.: Possible mechanisms of the beneficial action of glucocorticoids in circulatory shock. Surg. Gyne. and Obst., 137:597-607, 1973

2. Spath, J.A., Gorczynski, R.J. and Lefer, A.M.: Pancreatic perfusion in the pathophysiology of hemorrhagic shock. Amer. J. Physiol., 226:443-451, 1974

3. Gorczynski, R. J., Spath, J.A. and Lefer, A.M.: Vascular responsiveness of the in situ perfused dog pancreas. Europ. J. Pharmocol., 27:68-77, 1974

4. Gorczynski, R.J. and Lefer, A.M.: Properties of the reticuloendothelial system of the cat. Proceed. Soc. Exper. Biol. & Med., 147:24-28, 1974

5. Gorczynski, R.J., Klitzman, B.M. and Duling, B.R.: Interrelations between contracting striated muscle and precapillary microvessels. Amer. J. Physiol., 235:H494-H504, 1978

6. Gorczynski, R.J. and Duling, B.R.: The role of oxygen in arteriolar functional vasodilation in hamster striated muscle. Amer. J. Physiol., 235:H505-H515, 1978

7. Borgman, R.J., Erhardt, P.W., Gorczynski, R.J. and Anderson, W.G.: Cyclopropylamine hydrochloride (ASL-7003): A rigid analogy of dopamine. J. Pharm. Pharmacol., 30:193-195, 1978

8. Gorczynski, R.J., Anderson, W.G., Erhardt, P.W. and Stout, D.M.: Analysis of the cardiac stimulant properties of (3,4-dihydroxyphenyl)-cyclopropylamine (ASL-7003) and 2-Amino-6,7-Dihydroxy-1,2,3,4-Tetrahydronaphthalene (A6,7DTN). J. Pharm. Exp. Therap., 210(2):252-258, 1979

9. O'Donnell, J.P., Parehk, S., Borgman, R.J. and Gorczynski, R.J.: Synthesis and pharmacology of potential beta-blockers. J. Pharm. Science, 68(10):1236-1238, 1979

10. Erhardt, P.W., Gorczynski, R.J. and Anderson, W.G.: Conformational analogues of dopamine. Synthesis and pharmacological activity of (E)- and (Z)-2-(3,4 dihydroxyphenyl) cyclopropylamine hydrochlorides. J. Med. Chem., 22 (8):907-911, 1979

11. Reynolds, R.D. and Gorczynski, R.J.: Comparison of the autonomic effects of procainamide and N-acetylprocainamide in the dog. J. Pharm. Exp. Therap., 212:579-583, 1980

12. Reynolds, R.D., Burmeister, W.E., Gorczynski, R.J., Dickerson, D.D., Mathews, M.P. and Lee, R.J.: Effects of propranolol on myocardial infarct size with and without coronary artery reperfusion in the dog. Cardiovas. Res., 15 (8):411-420, 1981

13. Gorczynski, R.J., Anderson, W.G. and Stout, D.M.: N-aralkyl substitution of 2-amino-5,6-and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 1. Cardiac and pressor/depressor activities. J. Med. Chem., 24:835-839, 1981

14. Stout, D.M. and Gorczynski, R.J.: N-aralkyl substitution of 2-amino-5,6- and -6,78-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 2. Derivatives of a hypotensive-positive inotropic agent. J. Med. Chem., 25:326-328, 1982

15. Gorczynski, R.J.: Cardiovascular pharmacology of ASL-7022, a novel catecholamine. I. Inotropic, chronotropic and pressor actions. J. Pharm. Exp. Therap., 223 (1): 7-11, 1982

16. Gorczynski, R.J. and Wroble, R.W.: Cardiovascular pharmacology of ASL-7022. II. Mechanisms of inotropic selectivity. J. Pharm. Exp. Therap., 223 (1):12-19, 1982

17. Zaroslinski, J., Borgman, R.J., O'Donnell, J.P., Anderson, W.G., Erhardt, P.W., Kam, S-T, Reynolds, R.D., Lee, R. J. and Gorczynski, R.J.: Ultra-short acting beta-blockers: A proposal for the treatment of the critically ill patient. Life Sciences, 31:899-907, 1982

18. Erhardt, P.W., Woo, C.M., Gorczynski, R.J. and Anderson, W.G.: Ultra-short-acting beta-adrenergic receptor blocking agents. 1. (Aryloxy)propanolamines containing esters in the nitrogen substituent. J. Med. Chem., 25:1402-1407, 1982

19. Erhardt, P.W., Wood, C.M., Anderson, W.G. and Gorczynski, R.J.: Ultra-short-acting beta-adrenergic receptor blocking agents. 2. (Aryloxy)propanolamines containing esters on the aryl function. J. Med. Chem., 25:1408-1412, 1982

20. Klitzman, B., Damon, D.N., Gorczynski, R.J. and Duling, B.R.: Augmented tissue oxygen supply during striated muscle contraction in the hamster: Relative contributions of capillary recruitment, functional dilation and reduced tissue PO_2. Circulation Research, 51:711, 1982

21. Lee, R.J., Gorczynski, R.J. and Reynolds, R.D.: Screening methods and test models for evaluation of cardioactive drugs. Chem. Pharm. Drugs, 7:41-100, 1986

22. Gorczynski, R.J., Shaffer, J.E. and Lee, R.J.: Pharmacology of ASL-8052, a novel beta-adrenergic receptor antagonist with an ultrashort duration of action. J. Cardiovas. Pharm., 5:668-677, 1983

23. Gorczynski, R.J.: Cardiovascular pharmacology of ACC-9089 - A novel ultra-short-acting beta-adrenergic receptor antagonist. J. Cardiovas. Pharm., 6:555-564, 1984

24. Erhardt, P.W., Woo, C.M., Matier, W. L., Gorczynski, R.J. and Anderson, W.G.: Ultra-short-acting beta-adrenergic receptor blocking agents. 3. Ethylenediamine derivatives of (aryloxy)propanolamines having esters on the aryl function. J. Med. Chem., 26:1109-1112, 1983

25. Gorczynski, R. J. and Reynolds, R.D.: Cardiovascular pharmacology of ASL-7022, III. Peripheral vascular adrenergic mechanisms. J. Pharm. Exp. Therap., 232 (3):629-635, 1985

26. Kam, S-T., Matier, W.L., Mai, K.X., Barcelon-Yang, C., Borgman, R.J., O'Donnell, J.P., Stampfli, H.F., Sum, C.Y., Anderson, W.G., Gorczynski, R.J. and Lee, R.J.: [(Arylcarbonyl)oxy]propanolamines. 1. Novel beta-blockers with ultrashort duration of action. J. Med. Chem., 27-1007-1016, 1984

27. Kam, S-T., Matier, W.L., Mai, K.X., Anderson, W.G., Gorczynski, R.J. and Lee, R.J.: [(Arylcarbonyl)oxy]propanolamines: New catechol beta-blockers with little beta-intrinsic activity. J. Med. Chem., Sept., 1983

28. Gorczynski, R.J., Murthy, V.S. and Hwang, T.F.: Beta-blocking and hemodynamic effects of ASL-8052. J. Cardiovas. Pharm., 6:1048-1059, 1984

29. Shaffer, J.E. and Gorczynski, R.J.: Role of alpha-adrenergic receptors in the intrinsic inotropic selectivity of dobutamine in anesthetized dogs. Canad. J. Physiol. Pharm., 63 (6):630-635, 1985

30. Shaffer, J.E. Vuong, A., Gorczynski, R.J. and Matier, W.L.: In vitro and in vivo evaluation of two ultrashort-acting beta-adrenoreceptor antagonists: ACC-9129 and ACC-9369. Drug Develop. Res. 7:211-232, 1986

31. Murthy, V.S., Hwang, T.F., Rosen, L.B. and Gorczynski, R.J.: Controlled beta-receptor blockade with flestolol: a novel ultrashort-acting beta-blocker. J. Cardiovas. Pharm., 9(1):72-78, 1987

32. Gorczynski, R.J.: Basic pharmacology of esmolol. Amer. J. Cardiol., 56:3-13 F, 1985

33. Gorczynski, R.J., Quon, C.Y., Krasula, R.W. and Matier, W.L.: Esmolol: new drugs annual. Cardiovas. Drugs, 3:99.Ed. Alexander Scriabine. Raven Press: New York, 1985

34. Shaffer, J.E., Vuong, A., and Gorczynski, R.J.: Participation of the autonomic nervous system in the cardiovascular effect of milrinone. Life Sciences, 38-1967-1974, 1986

35. Sum, C.Y. and Gorczynski, R.J.: Pharmacokinetics and pharmacodynamics of esmolol, an ultra-short acting beta-blocker. J. Pharm. Exp. Therap

36. Brown, G.S., Gorczynski, R.J., Reynolds, R.D. and Shaffer, J.E.: Comparison of the parasympatholytic activity of ACC-9358 and disopyramide. Br. J. Pharm. 87:87-95, 1986

37. Reynolds, R.D., Gorczynski, R.J. and Quon, C.Y.: Pharmacology and pharmacokinetics of esmolol. J. Clin. Pharm., 26 (A): A3-A14, 1986

38. Quon, C.Y. and Gorczynski, R.J.: Pharmacodynamics and onset of action of esmolol in anesthetized dogs. J. Pharm. Exp. Therap., 237:912-8, 1986

39. Spokas, E.G., Suleymanov, O.D., Bittner, S.E., Campion J.G., Gorczynski, R.J., Lenaers, A. and Walsh, G.M.: Cardiovascular effects of chronic high-dose atriopeptin III infusion in normotensive rats. Toxicol. Appl. Pharm., 91:305-314, 1987

40. Nicholson, N.S., Panzer-Knodle, S.G., Salyers, A.K., Taite, B.B., King, L.W., Miyano, M.M., Gorczynski, R.J., Williams, M.H. Zupec, M.E., Tjoeng, F.S., Adams, S.P., Feigen, L.P., et al.: Antiplatelet and antithrombotic effects of platelet GPIIb/IIIa inhibition by arginine-glycine-aspartic acid-serine (RGDS) and arginine-glycine-aspartic acid (RGD) (O-me)Y (SC-46749). J. Pharm. Exp. Therap., 256 (3):876-882, 1991

41. Haskel, E.J., Adams, S.P., Feigen, L.P., Saffitz, J.E., Gorczynski, R.J., Sobel, B.E. and Abendschein, D.R.: Prevention of reoccluding platelet-rich thrombi in canine femoral arteries with a novel peptide antagonist of platelet GPIIb/IIIa receptors. Circulation, 80 (5): 1775-1782, 1989

42. Nicholson, N.S., Panzer-Knodle, S.G., Salyers, A.K., Taite, B.B., Miyano, M., Garland, R., Gorczynski, R.J., Williams, M., Zupec, M., Tsoeng, S. Adams, S.P., and Feigen, L.P.: In-vitro and In-vivo Effects of a Non-Peptide Analog (SC-47643) of RGD as an Antiplatelet and Antithrombotic Agent. Thrombosis Research 62:567-578, 1991

43. Panzer-Knodle, S., Nicholson, N.S., Taite, B.B., Gorczynski, R.J., and Feigen, L.P., Species variation in the effect of glycoprotein IIB./IIIa antagonists on inhibition of platelet aggregation. Journal Pharmacological Methods 30:47-53, 1993

44. Zuckerman, S.H., Doyle, M.P., Gorczynski, R.J., and Rosenthal, G.J.: Preclinical Biology of Recombinant Human Hemoglobin rHb1.1. Art. Cells, Blood Subs., and Immob. Biotech. 22:457-465, 1994

45. Sillerud, L.O., Caprihan, A., Fink-Berton, N., Springer, K., Rosenthal, G.J., and Gorczynski, R.J.: Efficacy of Recombinant Human Hemoglobin (rHb1.1) Determined by 31P NMR During Isovolemic Exchange Transfusion. Submitted, J. Appl. Physiology

46. Sillerud, L.O., Rosenthal, G.J., and Gorczynski, R.J.: Comparison of Optro^{tm} with Whole Blood. In preparation

47. William Freytag, Ph.D., Robert F. Caspari, M.D. and Richard J. Gorczynski, Ph.D.: Recent Progress in the Development of Recombinant Human Hemoglobin (rHb1.1) as an Oxygen Therapeutic, Tokyo, 1997

48. J. Craig Hartman, Gayle Argoudelis, Daniel Doherty, Douglas Lemon and Richard Gorczynski: Reduced nitric oxide reactivity of a new recombinant human hemoglobin attenuates gastric dysmotility. European Journal of Pharmacology 363: 175-178, 1998

49. Brian D.Lowes, Michael Higginbotham, Lawrence Petrovich, Marcus A. Dewood, Karl Weber, Mark A.Greenberg, Peter S. Rahko, G. William Dec, Thierry LeJemtel, Robert L. Roden, Margo M. Schleman, Alastair D. Robertson, Richard J. Gorczynski and Michael R. Bristow, for the Enoximone Study Group. Low Dose Enoximone Improves Exercise capacity in Chronic Heart failure. Submitted to : Journal of the Americam College of Cardiology, June, 1999.

ABSTRACTS

1. Gorczynski, R.J., Spath, J.A. and Lefer, A.M.: Lack of vasodilator action of synthetic glucocorticoids in circulatory shock. Circulation Suppl., 7-8:IV-107, 1973

2. Spath, J.A., Gorczynski, R.J. and Lefer, A.M.: Pathophysiologic changes associated with pancreatic hypoperfusion in hemorrhagic shock. Circulation Suppl., 7-8:IV-107, 1973

3. Gorczynski, R.J., Spath, J.A. and Lefer, A.M.: Vascular responsiveness of the perfused dog pancreas to vasoconstrictors and glucocorticoids. The Physiologist, 16:327, 1973

4. Spath, J.A., Gorczynski, R.J. and Lefer, A.M.: Relation of pancreatic ischemia and proteolysis to the pathogenesis or shock. The Physiologist, 16:460, 1973

5. Gorczynski, R.J. and Duling, B.R.: Functional vasodilatation of arterioles in striated muscle. Proceed., First World Cong. for Microcirculation, Toronto

6. Gorczynski, R.J. and Duling, B.R.: The role of oxygen in functional arteriolar vasodilatation. Federation Proc., 1976

7. Gorczynski, R.J. Anderson, W.G., Erhardt, P.W. and Stout, D.M.: The cardiac stimulant activity of (3,4-dihydroxyphenyl)-cyclopropylamine (ASL-7003) and A,6,7 DTN. Pharmacologist, 20:253, 1978

8. Ellis, D.J. and Gorczynski, R.J.: Cardiac and vascular action of prenalterol. Federation proc. 40, Part 1:662, 1981

9. Gorczynski, R.J. and Erhardt, P.W.: Mechanism of inotropic selectivity of indirect acting phenethylamines. Federation Proc. 40, Part I, 313, 1981

10. Gorczynski, R.J. and Lee, R.J.: Preclinical pharmacology of ASL-7022: A sympathomimetic positive inotropic agent with sympathoinhibitory properties. Presented at Annual Meeting of American College of Cardiology, April, 1982

11. Wilson, G.D. and Gorczynski, R.J.: Sympathoinhibitory properties of secondary-amino-aralkyl derivatives of 6,7 and 5,6 dihydroxyaminotetral in (A-6, 7-DTN and A-5, 6-DTN). Federation Proc. 41, 1060, 1982

12. Sum, C.Y., Lee, R.J., Yacobi, A. and Gorczynski, R.J.: Pharmacodynamics of ASL-8052-an ultra-short acting beta blocker (USABB) in anesthetized dogs. Federation Proc. 42, 1139, 1983

13. Gorczynski, R.J. Sharer, J.E. and Lee, R.J.: ASL-8052, an ultra-short acting beta-adrenergic blocking agent. Federation Proc. 42, 636, 1983

14. Murthy, V.S., Hwang, T.F., Gorczynski, R.J. and Schmidt, D.H.: Transient, controlled beta receptor blockade with ASL-8052, an ultra-short acting beta blocker. Federation Proc. 42, 1291, 1983

15. Gorczynski, R.J. and Reynolds, R.D.: Analysis of the peripheral vascular actions of ASL-7022, a novel catecholamine. Presented at the Annual ISHR meeting, Hilton Head, SC, Sept., 1983

16. Shaffer, J.E., Vuong, A. and Gorczynski, R.J.: Effect of hexamethonium on the inotropic selectivity of cardiotonic agents in vivo. Presented at the Annual FASEB meeting, Anaheim, CA, April, 1985

17. Hartman, J.C., Koerner, J., Lancaster, L. and Gorczynski, R.J.: In vivo calibration of a transit time ultrasound system for measuring ascending aorta volume flow (AF). Presented at the Annual ASPET meeting, Boston, MA, August, 1985

18. Shaffer, J.E., Gorczynski, R.J. and Matier, W.L.: Antiglaucoma potential of two ultra-short acting beta adrenoreceptor antagonists. Presented at the Annual ASPET meeting, Boston, MA, August, 1985

19. Nicholson, N.S., Taite, B.B., Panzer-Knodle, S.G., King, L.W., Salyers, A.K., Gorczynski, R.J. Adams, S.P. and Feigen, L.P.: Inhibition of GPIIb/IIIa (GPIIb/IIIa) by RGDS and RGD(O-Me)Y(SC-46749). Presented at the American Heart Atherosclerosis and Thrombosis Meeting, Keystone, CO, Feb., 1989

20. King, L.W., Panzer-Knodle, S.G., Bennett, S.M., Bell, L.D., Day, K.C. Steele, L., Gorczynski, R.J. and Feigen, L.P.: Characterization of an ex vivo rabbit method for examining properties of rtPAs. FASEB, 1989

21. Adams, S.P., Toeng, F.S., Fok, K.F., Zupec, M.E., Williams, M.H., Feigen, L.P., Knodle, S.G., Nicholson, N.S., Taite, B.B., Miyano, M.M. and Gorczynski, R.J.: Novel peptide analog antagonists of GPIIb/IIIa stabilized against proteolysis are active antiplatelet agents in vivo. Am. Chem. Soc., Med. Chem. Sec., April, 1989

22. Adams, S.P., Tjoeng, F.S., Fok, K.F., Zupec, M.E., Williams, M.H., Feigen, L.P., Nicholson, N.S., Panzer-Knodle, S.G., Taite, B.B., Garland, R. Miyano, M.M. and Gorczynski, R.J.: RGD analog antagonist of GPIIb/IIIa stabilized against proteolysis are active platelet aggregation inhibitors in vivo. Thromb. Haemost., 62, 106, 1989

23. Feigen, L.P., Nicholson, N.S., Panzer-Knodle, S.G., Salyers, A.K., Taite, B.B., Miyano, M.M., Gorczynski, R.J., Tjeong, F.S. and Adams, S.P.: Antiplatelet effects of SC-46749, an analog of the adhesive protein recognition sequence RGDS. Thromb. Haemost., 62, 47, 1989

24. Feigen, L.P., King, L.W., Panzer-Knodle, S.G., Bennett, S.M., Gorczynski, R.J., Steele, L., Day, K.C., Meyer, E., Wun, T.C., Warren, T. and Bell, L.D.: Characterization of MB-1018, a recombinant human tPA variant. Thromb. Haemost., 62, 543, 1989

25. King, L.W., Panzer-Knodle, S.G., Bennett, S.M., Bell, L.D., Day, K.C., Steele, L., Gorczynski, R.J. and Feigen, L.P.: Characterization of an ex vivo rabbit method for examining properties of rtPAs. FASEB, 3, 4, 1989

26. Adams, S.P., Tjoeng, F.S., Fok, K.F., Zupec, M.E., Williams, M.H., Feigen, L.F., Panzer-knodle, S.G., Nicholson, N.S., Taite, B.B., et al.: Novel peptide analog antagonists of GPIIb/IIIa stabilized against proteolysis are active antiplatelet agents in vivo. Am. Chem. Soc., 197 (0), 1989

27. Feigen, L.P., Nicholson, N.S., Taite, B.B., Panzer-Knodle, S.G., King, L.W., Salyers, A.K., Gorczynski, R.J. and Adams, S.P.: Inhibition of the platelet GPIIb/IIIa receptor by an analog to RGDS. FASEB, 3, 1989

28. Gorczynski, R., Doyle, M.,: Efficacy of Recombinant Human Hemoglobin to Restore Oxygen Consumption following Hemorrhage, presented at the 6th International Symposium on Blood Substitute, Montreal, 1996

29. Doyle, M., Sillerud, Gorczynski, R., Rosenthal, G.: Comparison of Optro with Whole Blood using 31 P-NMR Spectroscopy, presented at the 7th International Symposium on Blood Substitute, Tokyo, 1997

30. Doyle, M., Gorczynski, R., Rosenthal, G.: Efficiency of Tissue Oxygenation from HBOC Solutions: Experience with Recombinant Human HB (rHb1.1), presented at the 4th International Congress on the Immune Consequences of Trauma, Munich, 1997

31. Gorczynski, R., Doyle, M., Rosenthal, G., Zuckerman: Preclinical update on rHb1.1, presented at the 17th International Symposium on Intensive Care and Emergency Medicine, Brussels, 1997

REFERENCES

Available on request.